# Prognostic Markers in the Course of Primary Biliary Cirrhosis.

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# SUMMARY

The focus in this thesis is on prognostic factors in primary biliary cirrhosis (PBC). The patients who were subject of this study all came from a single Dutch centre and although the methodology employed to reach conclusions could be sophisticated, the substrate most often consisted of bedside findings and routine laboratory investigations.
The main object of prognosis in this chronic disease is forecasting the interval to death, enabling interventions at a timely interval before this ultimate event. Much can be learned from those who died from PBC or had PBC as a secondary cause of death and this thesis therefore starts with an analysis of PBC mortality figures in The Netherlands.

In **Chapter 1,** mortality figures from The Netherlands Central Bureau of Statistics were analysed for death from PBC (417 persons) and with PBC (179 persons), totalling 596 persons (6.3 per million inhabitants of 35 years and over). The female/male ratio was with 4.2, smaller than compared with the literature. In the South of the country there were significantly fewer deaths and in the North significantly more. The median age class at death was 70-74 and no person died below 35. In 1992, liver transplantation (LT) had nearly eliminated death from PBC in the age category 35-59. It was concluded that mortality from PBC mainly occurs in the old and very old, which asks for a more general approach and management and that LT had been effective in eliminating death from PBC at younger age.

In **Chapter 2,** the mortality data were analysed for the secondary causes of death, including diseases usually associated with PBC, cardiovascular risk and malignancies. The secondary causes of death originated from the circulatory, digestive and respiratory tracts and from malignancies. A 25-fold higher than expected incidence of hepatocellular carcinoma (more in persons under 60) and a 5-fold increase in diseases of the musculoskeletal system was found. There were no significant differences for malignancies or for diseases of the circulatory system, including ischaemic heart disease (which is important as hypercholesterolaemia is common in PBC). It is concluded that the study of mortality data led to findings which are important for diagnosis and management in the still living patients with PBC.

In **Chapter 3**, the Mayo model is validated in 83 Dutch PBC patients. In 1989, the Mayo Clinic developed a prognostic model for PBC which is based on routine clinicochemical parameters (serum albumin, serum bilirubin and prothrombin time), one clinical finding (oedema score) and age only. It has become the most widespread prognostic model for PBC. The Mayo model proved able to predict survival within low-, medium- and high-risk score groups and testing of the individual risk scores in a Cox regression model showed excellent results. Plasma sodium and platelet count were investigated for survival predicting properties in PBC: plasma sodium failed and thrombocytes passed. In high-risk patients a combination of the Mayo Model and platelet count could predict survival somewhat better than the original Mayo model. Using both the original and the modified models as mathematical background, liver transplantation (performed in a number of patients) was shown to have a beneficial effect on survival, but the models could not be used to predict before LT the length of survival post-transplantation. It is concluded that the Mayo model was successfully validated, and that the predicting role of platelet count should be further investigated.

In **Chapter 4**, a time-dependent Mayo model, based on updated risk score results in PBC patients was developed to predict short term survival at any time in the course of the disease, using the prognostic Mayo variables of the latest patient visit. This was felt needed as the Mayo model underestimated survival in the high-risk group of patients. In this study the updated model was tested using 1945 patient visits from 312 PBC patients admitted to the Mayo Clinic and independently 481 intervals from the earlier mentioned 83 Dutch PBC patients. The update model was superior to the original model for predicting short-term survival in both patient sets. It was concluded from this cross-validated study that the Mayo update model can be recommended for improving the accuracy of survival prediction during the two years after a patient visit.

In **Chapter 5**, the first occurrences of clinical findings (signs and major events), Mayo survival probabilities as well as the course of four cirrhosis severity assessment scores (Mayo, Campbell, Pugh and Ascites/ Nutritional State (ANS)) were studied 16-0.5 years prior to death in 32 Dutch PBC patients dying from PBC. Eighty-four percent (n=27) experienced a major clinical event, always in the period 6 years (median 1) prior to death. Signs were observed for the first time as early as 14 years before death but most often in the final 6 years. The prognosis of patients in whom a sign was detected and the more so in those who had had an event was significantly shorter than the overall outlook. Actual survival plotted

against estimated Mayo 50% survival was concordant with a plateau phase from -16 to -7 years before death falling off from -6 to -0.5. The estimated 50 % survival rate in the period -6 to -0.5 years correlated with all severity assessment scores (Mayo best with Campbell and Pugh). Based on clinical findings and severity assessment scores it was concluded that a steady state (lasting at least 10 years) was followed by a final phase (the last 6 years before death), which was marked by the appearance of events, and worsening of severity assessment scores which all showed a clear correlation to the Mayo survival estimates.

In **Chapter 6**, the additional prognostic value of clinicochemical parameters and body measurements was investigated in the 32 patients dying from PBC. Erythrocyte sedimentation rate and serum IgM were already elevated at the initial observation of all patients, indicating that our observation period did not encompass early PBC. Several laboratory parameters showed increased worsening in the last two years before death, which was coined the terminal phase. Sixty-seven items: clinicochemical variables, body measurement parameters, severity assessment scores, first observations of signs and first occurrences of major events were analysed by time-dependent Cox regression analysis for prediction of survival and of major events. Multivariate independent predictors of survival were for the steady state phase (-16 to -7 years) Campbell score, temperature and platelet count, for the final phase (-6 to -0.5) Mayo score and urinary sodium and for the terminal phase (-2 to -0.5) serum bilirubin and ANS-score. Independent predictors for the first occurrence of events were for ascites: Mayo risk score and plasma sodium, for hepatic encephalopathy: Mayo risk score, for upper gastrointestinal bleeding (and separately variceal bleeding): whole blood water and for any event: urinary sodium and serum IgA. It is concluded that four disease phases can be identified: early PBC (not in our patients), steady state (up to six years before death), a final phase (six years before death) and as part of this the terminal phase (the last two years). Independent predictors of survival could be identified for all phases present in our patients as well as for the major clinical events.

In **Chapter 7**, the (additional) prognostic value of antimitochondrial antibody subtypes was investigated in the 32 patients dying from PBC. Antimitochondrial antibodies are diagnostic for PBC and it has been proposed that their subtypes (and subtype profiles) are indicators for the progression of disease. A search for prognostic indicators of survival was done for the whole observation period, and the three disease phases (steady state, final and terminal) separately. When only the 55 auto-antibody parameters were subjected to Cox regression,

multivariate predictor in the steady state phase and the final phase was M8 (favourable), over the whole period M2 and M8 (favourable) and in the terminal phase none. When the subtypes were tested in combination with the clinicochemical parameters, they (together with clinicochemical parameters) appeared in the multivariate analysis over the whole period (M2) and the steady state (M8) but not in the final and terminal phases. In combination with the 67 clinicochemical and clinical parameters, mitochondrial antibody subtypes or profiles did not appear as predictors in the multivariate analysis in any phase of the disease. It was concluded that in this patient population and study design, M2 and M8 subtypes had prognostic significance, but that the prognostic relevance of severity assessment variables and scores, clinical findings and routine clinicochemical laboratory parameters was greater.

In **Chapter 8**, the timing of liver transplantation in a group of 41 PBC patients was projected on the timeline to death of the 32 patients dying from PBC, using the clinical and laboratory parameters as described in previous chapters. The LT timing had been done on clinical judgement. The method used was to sliderule the variables and score results one year before LT against the same data 1-6 years before death. The best fit was for first occurrences of major events and for assessment scores between 1 year before LT and 2 years before death, the difference being one year. This was also reflected in the first occurrences of events which all took place in the last 5 years before LT, compared to 6 years before death from PBC. The laboratory results were inconclusive. The Mayo survival probabilities 2 years before death and 1 year before LT did not differ between both groups and were too optimistic. It was concluded that clinical judgement had been adequate and that in addition to survival estimates and severity assessment scores, other parameters such as first occurrences of major events should be taken into account for the timing of LT.

In **Chapter 9**, the relations of plasma sodium and of whole blood - and plasma water to death from PBC were investigated in the 32 patients dying from PBC. A severely decreased plasma sodium is known to be associated with shortened survival ($Na_p$<130 mmol/l: 'dilutional' hyponatraemia), but less is known about hydraemia as a prognostic factor. Over the whole 16 year period before death, whole blood water, plasma water and plasma sodium were independent prognostic indicators. The water and sodium observations of the 32 patients dying from PBC and the 41 LT patients then were pooled, and score ranges for plasma sodium and whole blood water were made, 1-3 from better to worse. Between the 3 sodium scores and between the 3 hydraemia scores significant differences existed in intervals to:

death or - in most instances - LT, all severity assessment scores, Mayo survival probabilities and most laboratory parameters. Plasma sodium <130 was in a large minority not associated with hyperhydraemia and the term 'dilutional hyponatraemia' therefore is debatable. It was concluded that hyperhydraemia was a prognostic factor in our patients with PBC and that the well-known short survival in patients with severe hyponatraemia could be confirmed.

*Conclusions.*

Prognostication in primary biliary cirrhosis has reached a level of certainty that is helpful to the clinician. Still, there are patients in whom severity assessment methods or survival probabilities do not signal impending danger. This field should be investigated further. Some important prognostic parameters are difficult to include for a general survival probability method. An example is the very bad outlook for the relatively few, but easily identifiable patients with a very low sodium. The shortened survival in hyperhydraemic PBC patients should be validated. In the timing of liver transplantation, over-all clinical judgement proved to be adequate.